Muramyldipeptide-Ganglioside Gfpt1 Conjugates", Biochem (1?9): pp. 378-384 and Vangsted, et al. (1994) "New Serum Markers For Small-Cell Lung Cancer. I. The Ganglioside Fucosyl-GM1" Cancer Detection and Prevention 18(3):pp.221-229 in view of Kensil et al. (1991) "Separation and Characterization of Saponins With Adjuvant Activity From Quillaja Saponaria Molina Cortex", 146(2):pp.431-437. The Examiner stated that Applicants' arguments and amendments [i.e., in the Amendment In Response To July 9, 2001 Office Action, Information Disclosure Statement and Petition For a Three Month Extension of Time", filed January 29, 2002] have been considered but they are not persuasive. The Examiner further stated that Applicants argue that the claims have been amended to recite small cell lung cancer but that Applicants' amendments are not persuasive to withdraw the rejection.

In discussing the references cited, in combination, to reject Applicants' claims, the Examiner stated that Jennemann et al. teach the administration of a fucosylated GM1 ganglioside to conjugated KLH. The Examiner further stated that the reference also teaches that the administration of similar antigens with QS-21 was able to induce an immune response in humans in the treatment of melanomas. The Examiner also stated that it appeared that the previous Office Action was confusing with respect to Jennemann et al. and adjuvants such as Quill A or QS 21 in that the Action was meant to convey that Jennemann et al. does not teach QS 21 or Quill A in conjunction with fucosylated GM1. The Examiner additionally stated that the Vangsted et al. and Kensil et al. references provide the motivation and reasonable expectation of success of using a fucosylated GM1 ganglioside

conjugated to a carrier, and administered to a subject for preventing or treating small cell lung cancer.

Prior to discussing the references cited to reject the claims, Applicants submit that a brief, non-limiting summary of the invention as presently claimed is in order to assist in highlighting for the Examiner in the discussion which follows those features which serve to distinguish the claimed invention over the cited combination of references.

As recited, e.g., in claim 1 of the application, the invention is directed to a composition which comprises: (a) a conjugate of a fucosyl GM1 ganglioside derivative to an immunogenic protein, (b) a carbohydrate derived from the bark of a Quillaja saponaria Molina tree, and (c) a pharmaceutically acceptable carrier, the amounts of such conjugate and such adjuvant being effective to stimulate or enhance antibody production in a subject, and wherein, in the conjugate, the ganglioside derivative is conjugated to the immunogenic protein through a ceramide portion of the ganglioside.

Turning now to a discussion of the cited references, Jennemann et al. does disclose the administration of a fucosylated GM1 ganglioside conjugated to KLH. However, as specifically stated by the Examiner in the Office Action, "Jennemann does <u>not</u> teach QS 21 [i.e., a carbohydrate derived from the bark of a Quillaja saponaria Molina tree] or Quill A in conjugation with Fucosylated GM1." (Emphasis supplied by Applicants) Thus, the reference does not disclose the presence of, or even any usefulness for, one of

the components required by Applicants' claim 1.

In an effort to remedy this deficiency, and to supply the missing element, the Examiner additionally notes in the Office Action that, "Jennemann et al teaches the administration of a fucosylated GM1 ganglioside conjugated to KLH and also teach that the administration of similar antigens with QS-21 was able to induce an immune response in humans in the treatment of melanomas" (emphasis supplied by applicants), citing therefore to p. 363 of the Jennemann et al. paper. In reviewing the portion of the reference cited by the Examiner, Applicants note that the authors referred to a, "similar immune conjugate", not a conjugate incorporating a "similar antigen" as stated by the Examiner. That is to say that the conjugate used to treat melanomas was "similar" to Applicants' fucosylated GM1 ganglioside-KLH conjugate in that both such conjugates were composed of an antigen conjugated to the immunogenic protein KLH. However, no "similarity" is demonstrated by Jennemann et al. between a fucosylated GM1 ganglioside antigen as included in Applicants' claimed composition and as disclosed for use without QS-21 or Quill A in the reference, and the Glac 2 ganglioside antigen disclosed in Jennemann et al. as being used with a Quillaja saponaria Molina saponaria adjuvant [fraction QS 21]. Thus, the question whether a fucosylated GM-1 ganglioside is sufficiently "similar" to a Glac 2 ganglioside that the addition of "a carbohydrate derived from the bark of a Quillaja saponaria Molina tree" (see, e.g. Applicants' claim 1) would provide beneficial results with both gangliosides is not answered anywhere in Jennemann et al. Thus there is no teaching or

disclosure, other than the Examiner's unsupported supposition, that an adjuvant extracted from the Quillaja saponaria Molina tree would be useful with a fucosylated GM1 ganglioside as well as a Glac 2 ganglioside. Thus there is also no support for the conclusion which the Examiner draws from the cited reference, i.e., that the reference would suggest to one of ordinary skill in the art the inclusion of such an adjuvant with the conjugate of fucosylated GM-1 ganglioside to KLH. The only actual support for making the proposed substitution, i.e., for adding an adjuvant such as QS 21 to the fucosylated GM1 ganglioside-KLH conjugate, is the teaching found in the specification of Applicants' above-identified application. This teaching can not, under the applicable law, be relied upon to support an "obviousness" rejection under 35 U.S.C. §103(a). Clearly, therefore, Jennemann et al. by itself does not teach or suggest Applicants' claimed invention.

Turning next to the Vangsted et al. paper cited in combination with Jennemann et al., the subject reference is directed primarily to the use of the ganglioside Fucosyl-GM1 as a serum marker for small cell lung cancer ("SCLC"). Data is presented concerning the levels of the FucGM1 in sera from SCLC patients. Additionally, the diagnostic and prognostic values of FucGM1 are discussed, and the markers are evaluated in comparison to clinical parameters of the patients. The reference concludes that FucGM1 may be of prognostic value in SCLC. The reference further concludes that FucGM1 may serve as a target for antibody-dependent cellular cytoxicity ("ADCC") treatment of patients with SCLC, perhaps as an adjuvant therapy in established treatment

strategies.

Notwithstanding the conclusions reached by the authors of the Vangsted, et al. reference, i.e., that (1) Fucosyl-GM1 serves as a marker to the presence of SCLC, and that (2) Fucosyl-GM1 may, at some future date, be used in the treatment of SCLC, Applicants are constrained to point out that the reference is totally devoid of any suggestion: (1) to conjugate the Fucosyl-GM1 ganglioside to an immunogenic protein, (2) or to include with such a conjugate, as an adjuvant, a carbohydrate derived from the bark of Quillaja saponaria Molina tree. Moreover, even if, for the sake of argument, one of ordinary skill in this art were to find the conjugation of Fucosyl-GM1 with immunogenic protein suggested by the combination of the Vangsted et al. and the Jennemann et al. references, (despite the lack of a teaching or disclosure in the references themselves to suggest such combination as required under the applicable law), there is still no teaching or suggestion in the combination of references to include with such conjugate a carbohydrate derived from the bark of a Quillaja saponaria Molina tree. Thus, the combination of Jennemann et al. and Vangsted et al. also does not teach or even suggest the presently claimed invention.

The third reference cited in combination with the two above-discussed articles to reject Applicants' claims is the Kensil et al. reference. Kensil et al. report on the separation and characterization (with regard to adjuvant activity), of saponins extracted from the Quillaja saponaria Molina tree. The reference notes (p.431, col.2) that crude preparations of Quillaja saponins

have been used to boost response to, e.g., Keyhole Limpet Hemocyanin. There is no teaching or disclosure anywhere in the cited reference, however, to suggest that the Keyhole Limpet Hemocyanin be conjugated to a fucosyl-GM1 ganglioside as in Applicants' claimed composition. In fact, the reference is entirely silent with regard to any adjuvant effect of a Quillaja saponaria Molina adjuvant in a composition containing a ganglioside, much less a fucosyl ganglioside as specifically recited in Applicants' claim 1. The only suggestion to combine the subject Kensil et al. reference with either or both of Jennemann et al. and/or Vangsted et al. is that provided by Applicants' specification, who were themselves the first to discover the advantages provided by the claimed combination comprising:

a) a conjugate of a fucosyl GM1 ganglioside derivative to an immunogenic protein;

b) a carbohydrate derived from the bark of a Quillaja saponaria Molina tree; and

c) a pharmaceutically acceptable carrier.

Therefore, since the cited references neither teach nor even suggest the invention as presently claimed, whether taken individually or in any combination, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-2, 5-8 and 11-16 under 35 U.S.C.§103(a) to permit the subject claims to issue.

If a telephone interview would be of assistance in advancing prosecution of the application, Applicants' attorneys invite the Examiner to telephone at the number provided below.

No fee is believed to be due with this submission. Should any fee be due, however, authorization is hereby provided to charge the required amount to Deposit account No. 03-3125.

Respectfully submitted,

Mark A. Farley

John P. White
Registration No. 28,678
Mark A, Farley
Registration No. 33,170
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Mark A. Farley 7-16-02

John P. White Date
Reg. No. 28,678
Mark A. Farley
Reg. No. 33,170